Discovery and Characterization of 2-Aminooxazolines as Highly Potent, Selective, and Orally Active TAAR1 Agonists

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Ⓢ Supporting Information

ABSTRACT: 2-Aminooxazolines were discovered as a novel structural class of TAAR1 ligands. Starting from a known adrenergic compound **1**, structural modifications were made to obtain highly potent and selective TAAR1 ligands such as **12** (RO5166017), **18** (RO5256390), **36** (RO5203648), and **48** (RO5263397). These compounds exhibit drug-like physicochemical properties, have good oral bioavailability, and display *in vivo* activity in a variety of animal models relevant for psychiatric diseases and addiction.

KEYWORDS: TAAR1 agonist, 2-aminooxazoline, SAR, schizophrenia
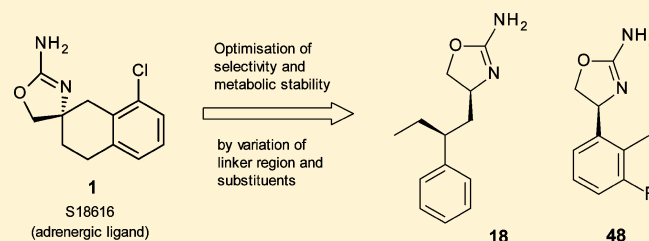
Trace amines (TAs) are metabolites of amino acids with structural similarity to biogenic amines and represent the endogenous ligands of the trace amine associated receptor 1 (TAAR1).[1,2] Dysregulation of TAs in the brain has been linked to a variety of psychiatric diseases and selective TAAR1 ligands have gained much interest as potential therapeutics for depression, schizophrenia, bipolar disorder, ADHD, and psychostimulant addiction.[3]

The modulatory role of this G protein-coupled receptor on monoaminergic neurotransmission has recently been investigated and confirmed by characterization of a transgenic mouse line overexpressing TAAR1 in central nervous system neurons.[4] Further efforts were made to identify potent and selective TAAR1 agonists with favorable pharmacokinetic properties in order to prove the modulatory effect on dopaminergic signaling *in vivo*.[5]

In an endeavor to discover a novel and selective TAAR1 chemotype, we considered application of the SOSA approach (Selective Optimization of Side Activities) to adrenergic ligands as a viable lead identification strategy.[6] Structural similarity of TAAR1 agonists with adrenergic agonists was already known from our previous work[5] pointing toward a similarity of the binding regions of both receptors.[7,8] Therefore, we searched the literature and in-house databases for adrenergic ligands reported as drugs or development candidates, whereupon the alpha 2 adrenergic receptor partial agonist S18616 from Servier (**1**) caught our attention.[9] Pleasingly, testing this candidate revealed (besides its expected activity at the human α_{2A} receptor) a high functional activity at human TAAR1 (EC$_{50}$ = 15 nM).[10]

A medicinal chemistry optimization program was then started aiming for compounds selective for TAAR1, where the known TAAR1 pharmacophore motif (aromatic moiety linked to a basic headgroup) of S18616 was kept, but the linker region was modified by opening the central six-membered ring (Figure 1). For all such derived compounds selectivity data was
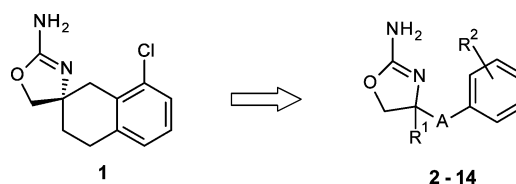

Figure 1. S18616 (**1**) and derived 2-aminooxazolines.

obtained by measuring functional activity at the human TAAR1 receptor (EC$_{50}$ hTAAR1) and in addition at the human adrenergic α_{2A} receptor (hα_{2A}) (Table 1).

All 2-aminooxazolines were synthesized from the corresponding amino alcohols **15** and cyanogen bromide in the presence of a base as depicted in Scheme 1. The enantiomerically pure amino alcohols were obtained from the chiral pool (e.g., via reduction of amino acids or their derivatives). The procedures are described in the Supporting Information.

We observed that the (*S*)-benzyl derivatives such as **2** or **3** showed functional activity at hTAAR1 but were not selective vs α_{2A} (Table 1). In contrast, the (*S*)-phenethyl derivatives such as **5** or **6** were much more potent hTAAR1 ligands and, surprisingly, showed promising selectivity vs the adrenergic receptor. An additional methyl substituent at the chiral center as in **7**, however, was less tolerated.

**Table 1. Yields, Functional Activity Data at hTAAR1, and Selectivity vs hα$_{2a}$ for Compounds 1−14**

compd	R^1	A	R^2	configuration	synthetic yield	hTAAR1 EC$_{50}$ (nM)	hTAAR1 E$_{max}$[a]	functional selectivity ratio hTAAR1 vs hα$_{2A}$
1						15	60%	0.047
2	H	CH$_2$	o-Cl	S	41%	154	100%	2.1
3	H	CH$_2$	H	S	66%	330	100%	1.3
4	H	CH$_2$	H	R	54%	2900	47%	n.d.
5	H	CH$_2$−CH$_2$	m-Cl	S	56%	18	87%	57
6	H	CH$_2$−CH$_2$	H	S	42%	27	72%	31
7	Me	CH$_2$−CH$_2$	m-Cl	S	21%	330	90%	2.0
8	H	CH$_2$−O	m-Cl	S	76%	270	90%	6.4
9	H	CH$_2$−NH−	m-Cl	S	60%	580	58%	4.8
10	H	CH$_2$−NMe−	m-Cl	S	47%	27	84%	3.8
11	H	CH$_2$−NEt−	m-Cl	S	41%	29	85%	38
12	H	CH$_2$−NEt−	H	S	53%	59	87%	36
13	H	CH$_2$−N^{i}Pr−	H	S	47%	140	58%	48
14	H	CH$_2$−NEt−	H	R	51%	230	94%	8

[a]The E$_{max}$ value describes the degree of functional activity compared to 100% for the natural ligand and full agonist phenethylamine.
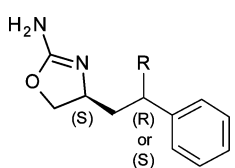
Scheme 1. Synthesis of 2-Aminooxazolines from 15[a]
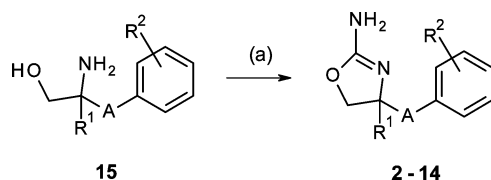
[a]Reagents and conditions: (a) BrCN, K$_2$CO$_3$, THF, RT, 18 h, 21−76%.

To establish further SAR and to avoid a metabolically labile benzylic position we investigated derivatives **8** to **14** where the benzylic carbon was replaced by oxygen or nitrogen. The N-alkyl derivatives **10−12** showed excellent functional TAAR1 activity, and we decided to characterize compound **12** further. Compound **12** (= RO5166017) exhibited high potency at mouse TAAR1 (EC$_{50}$ = 3 nM) and rat TAAR1 (EC$_{50}$ = 14 nM) as well, was highly selective (as evaluated from radioligand binding assays for a panel of other targets, performed at Cerep[11]), and was successfully used as the first tool compound from this new aminooxazoline class to be tested in mouse experiments.[12,13]

However, we observed high metabolic clearance of **12** in our second model species, the rat, which would limit the use of this compound in behavioral studies. We attributed this to the presence of the central C−N linker motif and could confirm N-dealkylation as the major metabolic pathway by metabolite ID.[10] In addition, testing **12** and analogues for GSH adduct formation, a screen for reactive metabolite formation,[14] revealed the pronounced formation of GSH adducts in vitro upon metabolic activation in both rat and human liver microsomes. These findings were attributed to the presence of the aniline structural motif, which is linked to reactive metabolite formation via oxidative generation of quinone imine intermediates.[15] Owing to foreseeable difficulties for clinical development of compounds, which might pose a risk for idiosyncratic toxicity due to reactive metabolite formation, we decided to reconsider carbon analogues, but this time introducing an additional methyl or ethyl substituent at the benzylic position as shown in Table 2.

Of these examples the (S,S)-ethyl-diastereomer **18** (= RO5256390) turned out to be a very potent full agonist at hTAAR1 and >500-fold selective vs α$_{2A}$. Evaluation in the

Table 2. Functional Activity Data at hTAAR1 and Selectivity vs hα$_{2a}$ for Compounds 16−19

| compd	R	hTAAR1 EC$_{50}$ (nM)	hTAAR1 E$_{max}$	sel. ratio vs hα$_{2a}$
16	(S)-Me	1540	79%	0.85
17	(R)-Me	730	84%	1.2
18	(S)-Et	18	98%	568
19	(R)-Et	2260	88%	3.5

Cerep[11] panel confirmed its selectivity against 155 other targets, and pharmacokinetic properties in mouse and rat were excellent making **18** an ideal tool for further behavioral tests.[16]

To access derivatives **16−19** a stereoselective synthesis was developed as depicted in Scheme 2 for compound **18**. Stereoselective pseudoephedrine enolate alkylation according to the methodology of Myers[17] and subsequent reduction yielded alcohol **26** in 91% ee, which was converted to iodide **27**. The second stereogenic center was introduced using Schöllkopf bis-lactimether methodology[18] (94% de for **29**). Chromatographic purification yielded amino ester **30**, which was converted in two steps to **18** (99.6% ee).
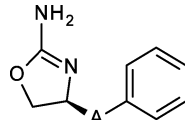
Having observed a strong influence of the linker region on activity at TAAR1 and on selectivity vs α$_{2A}$, we continued to make further variations in this part (see Table 3).

Interestingly, compounds with 3-atom-linkers were very active and selective as well (compounds **29** and **31**, Table 3). However, mainly due to observed increased in vitro metabolic clearance[10] of these rather flexible molecules we later abandoned this subseries in favor of the directly linked 2-amino-4-phenyloxazolines such as **32** (A = bond).

Figure 2 and Table 4 show a selection of substituents that we investigated for further optimization of these molecules.[19] Lipophilic substituents in o- and m-position increased activity at hTAAR1 (**33**, **34**), whereas substitution in p-position was less favorable (**35**, **37**). However, for high activity at rat TAAR1 (rTAAR1) p-substitution was favorable, and a combination of m- and p-substituents led to derivatives that showed a reduced species difference, such as compound **36**.

Scheme 2. Synthesis of 18 (RO5256390) by Application of Myers and Schöllkopf Methodology[a]
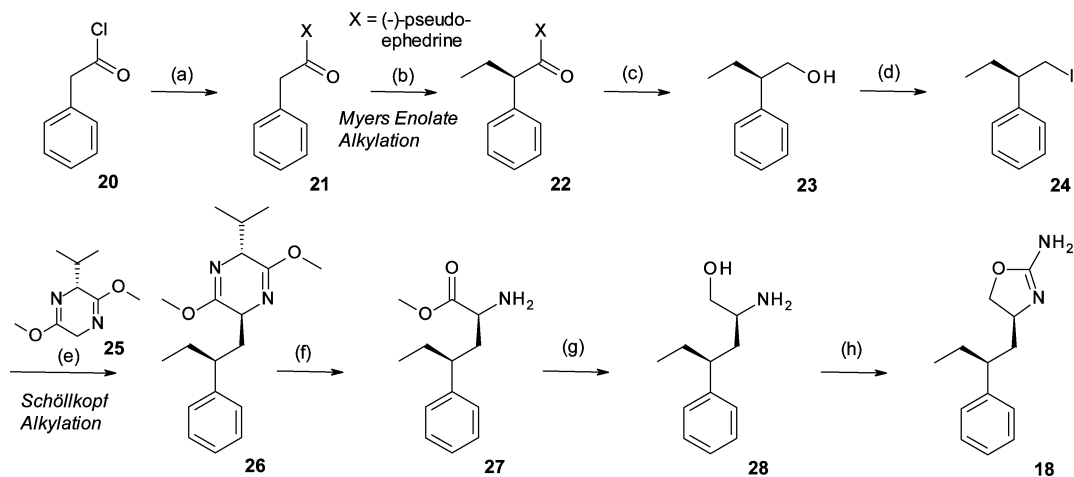
[a]Reagents and conditions: (a) (−)-pseudoephedrine, Et$_3$N, CH$_2$Cl$_2$, 96%; (b) LDA, LiCl, THF, −78 °C−RT, 99%; (c) LiH$_2$NBH$_3$, THF, RT, 0 °C−RT, 74%; (d) I$_2$, PPh$_3$, imidazole, CH$_2$Cl$_2$, RT, 91%; (e) (i) 25, n-BuLi, HMPA, THF, −78 °C, (ii) add 24, THF, −78−0 °C, 91%; (f) TFA, MeCN, H$_2$O, RT, chromat., 62%; (g) NaBH$_4$, EtOH, 60 °C, 88%; (h) BrCN, NaOAc, MeOH, 0 °C−RT, 60%.

Table 3. Functional Activity Data at hTAAR1 and Selectivity vs hα$_{2a}$ for Compounds 29−32

compd	A	hTAAR1 EC$_{50}$ (nM)	hTAAR1 E$_{max}$	sel. ratio
29	CH$_2$−CH$_2$−CH$_2$	27	86%	217
30	CH$_2$−O−CH$_2$	360	102%	n.d.
31	CH$_2$−CH$_2$−O	9	98%	818
32	bond	67	104%	670
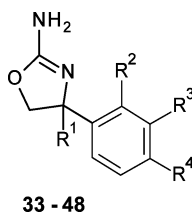
33 - 48

Figure 2. Substituted 2-amino-4-phenyloxazolines.

Activity was strongly dependent on stereochemistry, the (S)-isomer was always more active (37 vs 38). Additional substitution R^1 = Me on the aminooxazoline ring made the compounds more partial agonists at hTAAR1 (39, 40). Larger substituents in m- and p-position were detrimental (41, 42); fluorination was less tolerated as well (43). ortho-Alkyl substituents, however, especially in combination with p-chloro-substitution, led to the most active and selective compounds (45−47). The most selective compound was methyl fluoro derivative 48. Compounds 32−48 were synthesized from phenylglycinols in a similar way to that described in Scheme 1.

We first selected the partial agonist 36 (= RO5203648) for further studies. A Cerep screen[11] showed high selectivity across a panel of 149 enzymes and receptors, and pharmacokinetic analysis revealed that this compound was well suited for in vivo studies in rat. To our knowledge, 36 was the first selective partial TAAR1 agonist tested in behavioral studies, and it clearly demonstrated antipsychotic, antidepressant, and anti-addictive activities in a number of animal models.[20,21]

Unfortunately, additional in vitro testing of 36 revealed a very high metabolic clearance of this compound in human hepatocytes, which was not obvious in prior testing in human liver microsomes, and this led to a deselection of 36 for further development. These observations prompted us to compare in vitro microsomal clearance with in vitro hepatocyte clearance for a number of other compounds from the same series, whereby a surprisingly big discrepancy between the clearance data in the two assay systems was apparent for most of the compounds (Table 5).

In order to better understand the reasons for this discrepancy, we decided to elucidate unequivocally the metabolic clearance pathways by metabolite identification studies. The results indicated that N-glucuronidation, a comparatively rare metabolic transformation, occurred to a significant extent in human hepatocytes, being in most cases the primary clearance pathway for our 2-amino-4-phenyloxazoline compounds.[22]

N-Glucuronidation did not take place under the standard assay conditions for our routine in-house liver microsome clearance screening assay because the necessary cofactors for glucuronidation were not present. This appeared to be much less of an issue for metabolic clearance in rodents, where the primary route of metabolism was found to be oxidation, with the consequence that clearance data from the hepatocyte and microsome assays was generally in agreement.[10] Interestingly, for compound 18 from the other subseries very low clearance was confirmed in human hepatocytes, which we attributed to the increased steric demands of the branched linker present in compound 18.

Next we evaluated the propensity for the remaining compounds on our shortlist, namely, the compounds 40, 46, 47, and 48, which had medium clearance in human hepatocytes, to undergo covalent binding (CVB) to proteins during metabolism. Thus, in addition to the standard GSH adduct assay we measured covalent binding with ^{14}C-labeled material after metabolic activation in human liver microsomes and (since differences in metabolic clearances had been

Table 4. Functional Activity Data at Human TAAR1, Rat TAAR1, and Selectivity vs hα_{2a} for Compounds 33−48

compd	R^1	R^2	R^3	R^4	configuration	hTAAR1 EC$_{50}$ (nM)	hTAAR1 E$_{max}$	sel. ratio hTAAR1 vs hα_{2A}	rTAAR1 EC$_{50}$ (nM)	rTAAR1 E$_{max}$
33	H	Cl	H	H	S	23	100%	**115**	87	105%
34	H	H	Cl	H	S	21	73%	**333**	246	76%
35	H	H	H	Cl	S	143	64%	n.d.	52	64%
36	H	H	Cl	Cl	S	31	72%	**94**	8	58%
37	H	H	H	Br	S	150	93%	66	29	83%
38	H	H	H	Br	R	>10000		n.d.	n.d.	
39	Me	Cl	H	H	S	165	76%	6.4	560	62%
40	Me	H	H	Br	S	41	53%	**131**	18	36%
41	H	H	H	Ph	S	2670	24%	1.9	428	80%
42	H	H	OPh	H	R/S	1950	34%	n.d.	n.d.	
43	H	H	F	H	S	490	83%	n.d.	1920	68%
44	H	Me	H	H	S	67	78%	30	63	67%
45	H	Me	H	Cl	S	11	78%	**405**	1	93%
46	H	Et	H	Cl	S	26	83%	**115**	1	79%
47	H	cPr	H	Cl	S	12	77%	**400**	0.6	78%
48	H	Me	F	H	S	17	82%	**1800**	35	69%

Table 5. Comparison of *in Vitro* Clearance in Human Liver Microsomes (HLM) and in Human Hepatocytes (Hhep) for Compounds 36, 40, 45, 46, 47, 48, and 18

compd	CL HLM [mL/min/kg]	CL$_m$ class	CL Hhep [mL/min/kg]	CL$_h$ class
36	1.8	low	17.5	high
40	0	low	14.6	med
45	3.6	low	15	high
46	4.0	low	13	med
47	4.2	low	10.1	med
48	7.7	med	14	med
18	1.1	low	2.9	low

observed) in human hepatocytes as well (Table 6). The methyl-substituted aminooxazoline **40** showed the lowest CVB values,

Table 6. Measuring of Covalent Binding (CVB) after Metabolic Activation at Human Liver Microsomes (HLM) and Human Hepatocytes (Hhep) for Compounds 40, 46, 47, 48, and 18

compd	MCASE structural alert	GSH HLM assay (adduct)	CvB HLM [pmol/mg protein]	CvB Hhep [pmol/10^6 cells]
40	NEG	none	5	9
46	POS	none	2	42
47	POS	M + GSH^a	52	51
48	POS	M + GSH^a	29	32
18	POS	M + GSH^a	9	22

^{a}Slightly above detection limit.

which was in agreement with the classification by the *in silico* prediction tool MCASE[23] and consistent with the hypothesis that nucleophilic attack leading to opening the aminooxazoline ring can be diminished by introducing steric hindrance. For the other compounds including **18**, varying degrees of covalent binding were detected, with all compounds, however, well below 100 pmol/mg protein that constitutes a development concern in conjunction with a high clinical dose.[24]

After considering activity at hTAAR1, human hepatocyte clearance and applying further selection criteria such as inhibition of cytochrome isoforms (especially CYP2D6 with a 10-fold higher IC$_{50}$ compared to the other candidates) and

selectivity vs other receptors we finally selected compound **48** (= RO5263397) as the most promising development candidate for a partial TAAR1 agonist and confirmed the selectivity of **48** against 155 target proteins by performing a CEREP screen.[11]

Table 7 summarizes physicochemical and *in vitro* safety data for compounds **18** and **48**, which readily supported further

Table 7. Physicochemical and *in Vitro* Safety Characterisation of Compounds 18 (RO5256390) and 48 (RO5263397)

parameter	RO5256390	RO5263397
basic pK_a	8.98	8.07
Aq. solubility^a (μg/mL)	>4980	5830
logD at pH 7.4	1.29	1.12
PAMPA[25] P$_{eff}$ (10^{-6} cm/s)	10.7	14.5
hERG IC$_{20}$ (μM)	9.2	10.0
CYP 3A4/2D6/2C9 IC$_{50}$ (μM)	>50/3.6/>50	>50/32/>50
AMES/MNT	NEG/NEG	NEG/NEG
in vitro phototoxicity[26]	NEG	NEG

^{a}0.05 M phophate buffer, pH = 7.2−7.5, thermodynamic sol.

studies with these compounds. Pharmacokinetic analyses in rat, mouse, and cynomolgous monkey revealed very favorable *in vivo* properties, which have already been reported elsewhere.[16]

Testing both compounds in a variety of preclinical *in vivo* models revealed very interesting antipsychotic-like profiles.[16] The TAAR1 partial agonist **48** in addition increases wakefulness in rats and is active in the forced-swim test (FST) in rats indicative of potential antidepressant activity.[16] In addition, efficacy in reducing cocaine-mediated behaviors in animal models of substance abuse has recently been reported.[27−29]

In summary, we report here the discovery and optimization of 2-aminooxazolines as novel, selective, full and partial TAAR1 agonists. Starting from the known adrenergic ligand S18616 (**1**) and modifying the linker region and exploring additional SAR, we investigated several subseries of TAAR1 ligands. Besides functional activity at hTAAR1 and selectivity vs adrenergic α_{2A} receptor, metabolic stability measured in hepatocytes was used as a key parameter to finally select two molecules, **18** (RO5256390) and **48** (RO5263397), for further studies. Both compounds are active in a variety of behavioral models

for schizophrenia and drug addiction and have been selected as candidates for GLP toxicity studies.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchem-lett.5b00449.

> Experimental details for the synthesis of compounds 2–48 (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

TA, trace amine; TAAR1, trace amine associated receptor 1; h, human; r, rat; SAR, structure–activity relationship; SOSA, selective optimization of side activities; MCASE, Multiple Computer Automated Structural Evaluation; GSH, glutathion; CvB, covalent binding; HLM, human liver microsomes; Hhep, human hepatocytes; CL, clearance

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